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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,134	07/23/2003	Redford B. Williams JR.	5405.239CT	8271

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ART UNIT	**PAPER NUMBER**
1634	

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05/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,134	WILLIAMS, REDFORD B.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19 and 23-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,19 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/5/2007 has been entered.

2. Currently, claims 18-19, and 23-25 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is Non-FINAL.

Withdrawn Rejections

3. The rejection of claim 19 under 35 USC 112 first paragraph/written description is withdrawn in view of the amendment to the claim. Support for the claim is found in the specification at page 1, lines 29-30, page 2, page 10, figure 4, and claim 1 as originally filed.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 18-19 and 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18 and 19 are indefinite in the recitation of "increased". The recitation of "increased" is a relative term, and depends on what it is being compared to. In the instant claims, the claims do not make clear what the increased blood pressure is in comparison to. Additionally, the claim recites "increased" twice, such that when physiological response is "increased blood pressure", the substitution of this phrase for "physiological response" would read "increased increased blood pressure". At page 10, lines 6-7, the specification states that "subjects with at least one l allele ... show robustly larger MAP [mean arterial pressure] rises during stress periods". Accordingly, it is suggested that the claims be amended to recite:

--A method of identifying a human subject having an increased likelihood of having larger mean arterial pressure rises in response to psychological stress, comprising detecting the presence of at least one serotonin transporter gene promoter long allele in the human subject, wherein the detection of at least one serotonin transporter gene promoter long allele in the human subject identifies the human subject as having an increased likelihood of having larger mean arterial pressure rises in response to psychological stress, as compared to human subjects homozygous for the short allele.--

--A method of identifying a human subject having an increased likelihood of developing a cardiovascular disease in response to having larger mean arterial pressure rises in response to psychological stress, comprising detecting the presence of at least one serotonin transporter gene promoter long allele in the human subject, wherein the detection of at least one serotonin

transporter gene promoter long allele in the human subject identifies the human subject as having an increased likelihood of having larger mean arterial pressure rises in response to psychological stress and thereby as having an increased likelihood of developing a cardiovascular disease in response to having larger mean arterial pressure rises in response to psychological stress, as compared to human subjects homozygous for the short allele.--

Enablement

6. Claims 18-19 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening human subjects for increased risk of coronary heart disease in response to smoking by detecting the presence of at least one serotonin transporter gene promoter long allele, does not reasonably provide enablement for a method of identifying a human subject having an increased likelihood of having an increased physiological response to psychological stress or an increased likelihood of developing any cardiovascular disease in response to an increased physiological response to psychological stress by detecting the presence of at least one serotonin transporter gene promoter long allele as set forth in claims 18-19 and 23-25. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404, "Factors to be considered in determining whether a disclosure

would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Nature of the Invention and the breadth of the claims:

The claims are broadly drawn to a method of identifying a human subject having an increased likelihood of having an increased physiological response to psychological stress or an increased likelihood of developing any cardiovascular disease in response to an increased physiological response to psychological stress, wherein the physiological response is increased blood pressure, by detecting the presence of at least one serotonin transporter gene promoter long allele .

It is noted that although the specification is silent with regard to coronary heart disease (CHD), smoking, and the serotonin long allele, the art (Arinami et al; Thrombosis Haemostasis, vol. 81, pp 853-856, June 1999) is enabling for a method of screening human subjects for increased risk of CHD in response to smoking by detecting the presence of at least one serotonin transporter gene promoter long allele.

Amount of Direction and Guidance and presence and absence of working examples:

The specification asserts that the method of the invention comprises determining the presence of at least one, and preferably two serotonin transporter gene promoter long alleles in a

subject and that the presence of at least one and particularly two long alleles indicates the subject is at increased risk of disease as compared to a subject with no long alleles or with only one long allele (page 2). The specification teaches analyzing human subjects, not including those with medical or psychiatric disorders or current medication use, for 5HIAA levels (primary serotonin metabolite) in response to tryptophan depletion and response to the antagonist pindolol. The specification further analyzes differences in biological responses to tryptophan depletion or infusion, such as heart rate, mean arterial pressure, epinephrine and norepinephrine levels, cortisol levels, and prolactin levels in subjects with either short or long serotonin transporter gene promoter polymorphisms.

The specification teaches at page 10 and Figure 4, that subjects with at least one long allele showed larger mean arterial pressure rises during stress as compared to subjects homozygous for the short allele ($p< 0.001$). However, the specification is silent as to whether such levels are predictive in males and females.

Level of predictability and unpredictability in the art:

The post filing date art demonstrates the unpredictability of serotonin promoter alleles and stress. For example, while Rozanski teaches that depression contributes to coronary artery disease (Rozanski et al; Circulation, vol. 99, pages 2192-2217; 1999, see abstract), Kendler (Kendler et al; Arch. Gen. Psychiatry, vol. 62, May 2005, pages 529-535) teaches a study which analyzed the association between serotonin transporter promoter short and long alleles, stressful life events, and depression. Kendler teaches that individuals with two short alleles had an association between low threat event stress and depression. In contrast, Rozanski (Rozanski et

al; Circulation, vol. 99, pages 2192-2217) teaches that depression contributes to coronary artery disease (see abstract). Additionally, Grabe (Grabe et al; Molecular Psychiatry, vol. 10, pages 220-224; 2005) teaches that gene-environment interactions were studied in males and females for the serotonin transporter promoter alleles. Grabe teaches that the short allele showed an interaction with life stressors in females but not in males (page 223, col. 1, first sentence). Accordingly, it appears that associations between mental distress in females and the serotonin transporter alleles is not predictably correlative in males and females. Additionally, applicants own post filing date art (Williams et al; Neuropsychopharmacology, 2003, vol. 28, pages 533-541) teaches an analysis of CNS serotonergic function and serotonin related gene polymorphisms, including serotonin transporter promoter short and long alleles, and teaches that the effects of serotonin related gene polymorphisms on CNS serotonergic function vary as a function of both ethnicity and gender. Further, Williams teaches that the ss genotype is associated with higher 5HIAA levels in African Americans, but with lower levels in Caucasians. Williams teaches that the ss genotype is associated with higher 5HIAA levels in women but with lower levels among men (page 539, col. 1). Accordingly, the correlation between 5HIAA levels and serotonin promoter polymorphism genotype is not as predictable as asserted in the specification. Williams specifically teaches that "Further research will be required to determine the mechanisms underlying these differential effects. In the meanwhile, both ethnicity and gender should be taken into account in research evaluating effects of these and related polymorphisms on CNS serotonergic function, as well as the broad range of biological and behavioral functions that are regulated by CNS serotonergic function." (see abstract). However,

the instant specification provides no assessment as to ethnicity or gender with regard to the data presented and fails to support the broad scope of the claims directed to "any" subject.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of Experimentation necessary:

Given the evidence of unpredictability set forth in the art, unpredictable trial and error experimentation would be required of the skilled artisan to practice the invention commensurate in scope with the claims. To be able to practice the invention as broadly as it is claimed, the skilled artisan would have to perform a large number of studies, that included a sufficient number of both male and female subjects and matched controls to determine if the effect of psychological stress on blood pressure was predictably correlated in males and females. Given that he the specification lacks guidance to such correlation and that the art provides evidence of unpredictability with regard to correlating phenotypic associations with the long and short alleles of the serotonin transporter promoter polymorphism in males vs females, such analysis would be replete with unpredictable trial and error analysis, which is considered undue.

Conclusion:

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the negative teachings in the prior

art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to make or use the methods of the claims as broadly written.

Response To Arguments

6. The response traverses the rejection. The response as well as the declaration by Dr. Redford Williams submitted under 37 CFR 1.132 have been thoroughly reviewed. The evidence in the declaration regarding ethnicity was persuasive with regard to the issues raised in the previous office action. However, the data regarding a correlation in females does not appear to support the conclusion that "the association between 5HTTLPR genotypes and cardiovascular reactivity to psychological stress did not differ in men and woman". Panel A on page 4 of the declaration shows that the change in SBP was the same for women with the s/s and the s/l allele alleles. Additionally, it is not clear from the declaration whether the difference between s/s vs s/l & l/l was statistically significant in men or women, whereas figure 4 of the instant application shows a statistically significant association between the larger rise in MAP in l/l and l/s individuals vs s/s individuals. Additionally, for Panel A on page 5, the declaration does not state whether the results were statistically significant. Although there appears to be an increase from s/s to s/l to l/l individuals for the change in DBP, the error bars for the s/s and s/l appear to overlap in women. Accordingly, the evidence presented does not appear to show that women with at least one long allele are at increased risk of increased blood pressure in response to psychological stress broadly encompassed by the claims. The declaration additionally cites the post filing date art of Fumeron (2001) and Coto (2003) as "two other scientific groups provide

data that demonstrate that the presence of the 5HTTPLR L allele is associated with cardiovascular disease". The references have been thoroughly reviewed but were not found persuasive to overcome the rejection. Firstly, Fumeron teaches that the association found was with regard to subjects homozygous for the long allele, whereas the instantly pending claims are directed to "at least one long allele". Additionally, neither reference appears to take into account the unpredictability of gender associations as noted by Applicant's post filing date work and the teachings of Grabe cited in the rejection above. The issues raised in the response have been addressed in the enablement rejection above as well as the discussion of the declaration above. The rejection is maintained for these reasons.

Claim Rejections - 35 USC § 102

7. Claims 18-19, and 23-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Arinami et al., (Thrombosis Haemostasis, vol. 81, pp 853-856, June 1999) as defined by Grassi et al (Circulation, vol 90, pp 248-253, 1994).

Claim 18 is drawn to a method of identifying a human subject as having an increased likelihood of having an increased physiological response, which is increased blood pressure, in response to psychological stress by detecting at least one serotonin transporter long allele. Claim 19 is drawn to a method of identifying a human subject as having an increased likelihood of developing a cardiovascular disease in response to an increased physiological response to psychological stress as for claim 18. However, the claims recites "whereby the presence of at least one serotonin transporter gene promoter long allele..." which refers to a property of the polymorphism rather than the detection of the polymorphism in the human subject. The only

steps involves detecting the allele. The whereby clause is not given any weight as it appears to refer to a property of the polymorphism, rather than the detection step to identify a human subject as having an increased likelihood of having an increased physiological response [or of developing a cardiovascular disease]. Therefore, the following rejection under 35 USC 102(b) is set forth. The rejection can be overcome by amending the claims as set forth in the 112/2nd rejection above.

Arinami teaches analyzing patients with coronary artery disease for a serotonin transporter gene promoter polymorphism (see abstract, pp 853-854). Arinami teaches that the L allele (the long allele) was observed more frequently in patients with coronary heart disease ($p < 0.03$) and that this association was stronger ($p < 0.003$) in patients that also smoked. As defined by Grassi et al (abstract, col. 1, lines 18-22) smoking markedly and significantly increased mean arterial pressure, heart rate, calf vascular resistance, and plasma norepinephrine and epinephrine levels. The teachings of Arinami teach a study which identifies subjects with at least one serotonin transporter long allele as having an increased risk of cardiovascular disease.

8. Claims 18-19, and 23-25 are rejected under 35 U.S.C. 102(e) and 102(b) as being anticipated, in the alternative, by Comings I (Comings et al; US Patent 6,653,073) and Comings II (Comings et al; WO 99/42619).

Claim 18 is drawn to a method of identifying a human subject as having an increased likelihood of having an increased physiological response, which is increased blood pressure, in response to psychological stress by detecting at least one serotonin transporter long allele. Claim 19 is drawn to a method of identifying a human subject as having an increased likelihood of

developing a cardiovascular disease in response to an increased physiological response to psychological stress as for claim 18. However, the claims recites "whereby the presence of at least one serotonin transporter gene promoter long allele..." which refers to a property of the polymorphism rather than the detection of the polymorphism in the human subject. The only steps involves detecting the allele. The whereby clause is not given any weight as it appears to refer to a property of the polymorphism, rather than the detection step to identify a human subject as having an increased likelihood of having an increased physiological response [or of developing a cardiovascular disease]. Therefore, the following rejection under 35 USC 102(b) is set forth. The rejection can be overcome by amending the claims as set forth in the 112/2nd rejection above.

Comings I and II teach a method of identifying a subject at increased risk of developing elevated cholesterol, angina, and heart attach by detecting subjects heterozygous for the LS allele in the serotonin transporter gene.

Response to Arguments

9. Arguments with regard to priority and the rejection under 35 USC 102(b) will be addressed together. The entire '390 application has been thoroughly reviewed again, but was not found to support the claims presently pending. As stated in MPEP 2163.04: "The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. Wertheim, 541 F.2d at 263, 191 USPQ at 97."

It is noted that the examiner indicated in the interview of December 18, 2006, that claim 18 appeared to be supported in the '390 provisional application given the data at page 4. However, upon close review of the data at page 4, it is noted that the '390 application teaches, at lines 27-28 "larger heart rage... and blood pressure...reactivity to stress". In other words, at page 4, the '390 application teaches that blood pressure was more reactive to stress, it does not state that the blood pressure increased. The reactivity could have been that blood pressure was more erratic over a specific period of time, in response to the stress, or that the blood pressure decreased vs no change. As already noted in the previous office action and in the interview, the "Summary of the Invention" of the '390 application, clearly states that "In one particular embodiment, the method comprises determining the presence of **at least one (and preferably two) serotonin transporter gene promoter short alleles... indicates that said subject is at increased risk of disease, as compared to a subject with no short alleles or a subject with only one short allele**". No alternative embodiment is set forth. Therefore, this section of the Summary makes the opposite conclusion as that encompassed by the claimed invention. The response asserts that the reference to the short allele was an inadvertent typographical error. This argument has been thoroughly reviewed but was not found persuasive. In the instant case, the response provides no reasoning as to why the skilled artisan would have recognized the error as well as the appropriate correction. Therefore, when the specification of the '390 application is taken as a whole, the "Summary of the Invention" teaches that the invention is directed to detecting at least one, and preferably two, short alleles as indicative that a subject is at increased risk of disease. Although the statement "increased blood pressure" is made at page 2, line 21, this appears to be an example of a possible stress response, not an indication that it was the stress

response identified in the example. The only example found in the '390 application, as noted above, teaches that subject with high 5HIAA levels had "larger heart rage... and blood pressure...reactivity to stress", but does not teach that the blood pressure was increased. This correlation is made with regard to 5HIAA levels, not directly to genotype. Although the '390 application states that "Both high 5HIAA levels and the 'l' genotype show a similar pattern of association with cardiovascular and cortisol reactivity and/or levels" as noted with regard to the rejection under 112/first paragraph, enablement, the post filing date art teaches that 5HIAA levels were not predictable in males vs females, or with regard to ethnicity. The declaration submitted under 37 CFR 1.132 by Dr. William has been thoroughly reviewed, however the teachings of the prior art do not supplement critical omissions from the '390 application. None of the references cited at pages 2-3 provide any teachings of subjects with at least one long allele having increased blood pressure in response to psychological stress. Accordingly, the preponderance of the evidence indicates that the '390 application does not provide descriptive or enabling support for the instantly pending claims.

10. Claims 18, 19, and 23-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Hanna (Hanna et al; Neuropsychopharmacology, vol 18, February 1998, pages 102-111).

Claim 18 is drawn to a method of identifying a human subject as having an increased likelihood of having an increased physiological response, which is increased blood pressure, in response to psychological stress by detecting at least one serotonin transporter long allele. Claim 19 is drawn to a method of identifying a human subject as having an increased likelihood of developing a cardiovascular disease in response to an increased physiological response to

psychological stress as for claim 18. However, the claims recites "whereby the presence of at least one serotonin transporter gene promoter long allele..." which refers to a property of the polymorphism rather than the detection of the polymorphism in the human subject. The only steps involves detecting the allele. The whereby clause is not given any weight as it appears to refer to a property of the polymorphism, rather than the detection step to identify a human subject as having an increased likelihood of having an increased physiological response [or of developing a cardiovascular disease]. Therefor, the following rejection under 35 USC 102(b) is set forth. The rejection can be overcome by amending claims 18 and 19 as set forth in the 112/2nd rejection above.

Hanna teaches that subjects were analyzed for blood 5-HT levels and that the 5-HTT genotype was analyzed for association with seasonal variation (see page 108, col. 1). Hanna teaches that subjects with the ll genotype for 5-HTT transporter had significant seasonal differences in blood 5-HT levels whereas subjects with the ls genotype did not (abstract, page 107, para bridging cols 1 and 2).

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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4/26/07